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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,868	08/17/2006	Christopher Luckhurst	06275-468US1 100949-1P US	4699

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EXAMINER	
CHANDRAKUMAR, NIZAL S	
ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
12/24/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/549,868	LUCKHURST ET AL.	
	Examiner	Art Unit	
	NIZAL S. CHANDRAKUMAR	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/01/2008/08/05/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/01/2008 has been entered.

New IDS filed 08/05/2008 and 05/01/2008 were considered.

Claims 22-26 are pending.

Response to Applicants Remarks:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In view of applicant's remarks, previously presented rejection of claims 22-26 under 35 U.S.C. 112, first paragraph as failing to comply with the written description

requirement is recast as scope of enablement rejection. Response to applicant's remarks is found throughout this new rejection.

Claims 22-26 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for few compounds encompassed by the formula (I), does not reasonably provide enablement for wide variety of structural possibilities claimed. *For example,* the specification is not enabling for compounds when the benzoic acid or its derivative corresponding to the Y containing ring on the right hand side of formula I is SO3H. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the relevant factual considerations.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art.

All of the factors have been considered with regard to the claims, with the most relevant factors discussed below:

The chemistry direction provided in the specification for making the claimed

compounds is limited. It is not seen where in the specification enabling disclosure is found for making compounds wherein Y is

SO_3H, $CH_2CO_2R^3$, CH_2SO_3H, $OCH_2CO_2R^3$ or OCH_2SO_3H; or Z1, Z2 or Z3 is independently

alkyl (optionally substituted with halogen), C_{1-6} alkoxy (optionally substituted with halogen), $S(O)_p(C_{1-6}$ alkyl), $S(O)_qCF_3$ or $S(O)_2NR^6R^7$;

The direction, guidance and working example found in the specification for making such compounds is misleading at best, because there is no prior art citations or teaching in the specification for making benzoic acid (or its derivatives) needed for the amidation reaction to make compounds of formula (I). The working examples are misleading because the description in the working examples omits essential materials.

Applicants argue that the materials omitted from the specification pertaining to the preparation of the claimed compounds occurred due to clerical errors. Further, Applicant state that one skilled in the art could readily recognize these errors and would consult literature for clarification, and the references. In support of these assertions, applicant draws Examiner' attention to page 21, lines 4-5 and page 27, lines 6-7, page 21, lines 8-11 and page 27, lines 10-13.

Examiner's Response:

Clerical errors and literature teaching. The omitted materials are critical to the successful making of the compounds. There are two key steps in the making of the compounds. In the first step the benzoic acid portion (Y and Z containing fragment) is prepared. In the second step the benzoic acid is coupled to a 4-substituted piperidine.

The direction, guidance and working examples for carrying out these steps present in the specification is not adequate. The predictability and state of the art of organic chemistry is such that, consulting prior art would not adequately compensate for the lack of written description requirement. The unpredictability of in organic synthesis is high in spite of the high skill level in the area. The state of the art of organic chemical synthesis is closer to what is described by Dorwald et al. who states, "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work……Chemists tend not to publish negative results, because these are, as opposed

to positive results, never definite (and far too copious) [preface].....even structurally simple compounds often turn out not to be so easy to make as initially thought. [pg. 2]..... As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures [pg. 3]..... As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of a given starting material, and unexpected products may readily be formed. [8].....Even the most experienced chemist will not be able to foresee all potential pitfalls of a synthesis, especially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even simple chemical transformations can no longer be performed. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity [pg. 9]....." Dorwald F. A. Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface pg. 1-15. In addition, with regard to 'amidation reaction' applicant is state that one of ordinary skill in the art could readily recognize that the appropriate carboxylic acid needed. "In sum" the applicant states 'it is clear that one skilled in the art could readily identify the missing elements in the descriptions of the preparation of Intermediate 6 and Example 8. Indeed, the Examiner was able to do so without any difficulty. It follows that one skilled in the art could readily understand that Applicants had successfully prepared these two compounds and therefore had possession of them. Thus, the specification provides adequate written

description of these two compounds". Applicant continues to argue, citing MPEP2163.02, that 1) there is reasonable clarity in the specification and that 2) the applicant had possession of the invention as shown by the disclosure of structural formulae that the invention was complete etc.

This following was found on the cited pages:

page 21, lines 4-5 shown below

> (v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin);

are not relevant to the issues at hand. For example the WO documents describe compounds that do not fall under the claimed formula. These references do not teach how to make the instant compounds.

page 27, lines 6-7

EXAMPLE 8

This Example illustrates the preparation of methyl 2-[[4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidinyl]carbonyl]-4-methoxybenzoate.

4-(3,4-Dichlorophenoxy)-1-(4-piperidinylmethyl)-piperidine (343mg), EDCI (286mg), HOBT (135mg), DMAP (122mg) were dissolved in dichloromethane (20mL) and triethylamine (0.3mL) was added. The reaction mixture was stirred for 72 h. The solvents were evaporated and the residue was purified by RPHPLC (gradient 95% - 5% aqueous ammonium acetate, 5% - 95% acetonitrile) to give the title compound (30 mg).

MS $[M+H]^+$ (ES+) 535/537.

The inadequacy of what is found here is one of the bases of the rejection. The mass spectral numbers (M+H) are available for any structure without having possession of the compound.

See page 21, lines 8-11

bevacizumab, compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin);

(vi) vascular damaging agents such as combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

are not relevant to the issues at hand. For example the WO documents describe compounds that do not fall under the claimed formula.

page 27, lines 10-13

4-(3,4-Dichlorophenoxy)-1-(4-piperidinylmethyl)-piperidine (343mg), EDCI (286mg), HOBT (135mg), DMAP (122mg) were dissolved in dichloromethane (20mL) and triethylamine (0.3mL) was added. The reaction mixture was stirred for 72 h. The solvents were evaporated and the residue was purified by RPHPLC (gradient 95% - 5% aqueous ammonium acetate, 5% - 95% acetonitrile) to give the title compound (30 mg).

MS $[M+H]^+$ (ES+) 535/537.

The following Examples were prepared analogously to Example 8 from the appropriate acids and amines.

Example	Name (M+H)	^{1}H NMR δ(CD_3OD)
9	Methyl 4-[[4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidinyl]carbonyl]-benzoate (505/507)	

See above. These lines are not relevant to the issues at hand.

For the reasons presented above, there is a substantial gap between what is taught in the specification and what is being claimed. As such, one of ordinary skill in the art would be faced with undue amount of experimentation to identify compound(s) buried in the wide variety of possibilities encompassed by the formula (I). The specification lacks disclosure sufficient to make and use the invention commensurate with the scope of the claims.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation would be required to make and use Applicants' invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claims 22-26 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIZAL S. CHANDRAKUMAR whose telephone number is (571)272-6202. The examiner can normally be reached on 8.30 AM - 4.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571 0272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nizal S. Chandrakumar

/D. Margaret Seaman/

Primary Examiner, Art Unit 1625